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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/936,534	02/03/2003	Catia Bastioli	13929/T/B/A	7100

7590 05/18/2006

Bryan Cave
245 Park Avenue
New York, NY 10167

EXAMINER

PEARSE, ADEPEJU OMOLOLA

ART UNIT PAPER NUMBER

1761

DATE MAILED: 05/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/936,534

Applicant(s)

BASTIOLI ET AL.

Examiner

Adepeju Pearse

Art Unit

1761

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 March 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,4,7 and 10-14 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,4,7 and 10-14 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☒ None of:
- 1) ☒ Certified copies of the priority documents have been received.
 - 2) ☐ Certified copies of the priority documents have been received in Application No. _____.
 - 3) ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>1/15/2002</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Response to Arguments

1. Applicant argues that Van Loo is not a proper reference. However, applicant has not submitted copies of the foreign document or an official translation to the foreign document in order to perfect the requirements to overcome the reference. In any event, examiner submits a WO 98/52578, which is an equivalent of the US document to Van Loo for consideration.

1. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, applicant argues that there is no motivation to combine the teachings of the applied references. Claim 1 of the instant application recites chewable articles for animals being made from inulin or mixtures of inulin and/or oligofructans with thermoplastic polymers. Leo discloses in (Col 1, lines 28-31) an article for pets, specifically dogs and cats made from starch with a thermoplastic polymer. However, Leo does not show an article made from inulin. Van Loo teaches a fructan preferably inulin containing composition for the prevention and treatment of colon cancer in a non-bovine mammal (abstract). This composition is a functional food and can be present in any known food form including pet food (col 5 lines 42-50). It would be obvious to one of ordinary skill in the art to modify Leo with the teachings of Van Loo by incorporating inulin as an ingredient for cancer prevention as disclosed. The reason or motivation

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to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. In re Linter, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972).

2. Applicant argues that neither Van Loo nor Tomka disclose that inulin or mixtures of inulin with thermoplastic polymers can be thermoplastically processed. However, product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Claims 1-2, 4, 7 and 10-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leo (U.S. Pat. No. 5,419,283) in view of Van Loo et al. (U.S. Patent Number 6,500,805

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B2/WO 98/52578)), Guttag (U.S. Pat. No. 5,346,929) and Tomka (U.S. Pat. No. 5,844,023). The references and rejections are incorporated as cited in the previous office action. Applicant's arguments filed 3/16/2006 have been fully considered but they are not persuasive.

6. With regards to claims 4 and 10, Leo discloses in (col 2, lines 59-62), an article made from a degradable polymer consisting of starch.

7. With regard to claim 7, Leo discloses plasticizers including sorbitol and glycerol (col 1 lines 49-54).

8. With regard to claim 11, Leo discloses a chew toy for animals comprising a starch material and a biodegradable thermoplastic polymer. The starch is present at a range from 10-40% by weight (col 1 lines 33-35). However, Leo failed to disclose Inulin. Guttag teaches biodegradable plastic articles such as toys (col 3 lines 40-44) comprising a synthetic plastic polymer, a natural polymer and a polymer attacking agent. The natural polymers are found in nature and are easily broken down by natural decay bacteria. It includes but is not limited to particles of starch, inulin, cellulose and wood (col 2 lines 31-34). This suggests that starch and inulin are obvious equivalents as natural polymers and one of ordinary skill in the art would be able to utilize inulin in forming a toy/chewable article because it is easily broken down by natural decay bacteria.

9. With regard to claim 12, Leo discloses an animal chew toy obtained by processing starch and a thermoplastic polymer in the presence of water or a plasticizer under extrusion coking conditions (col 1 lines 33-41). However, Leo failed to disclose a temperature range for the process or inulin. Tomka teaches a biodegradable polymer mixture consisting of starch and a thermoplastic polymer. The mixture is extruded at a range of temperatures from 80°C to 190°C

(col 15 lines 50-54). Guttag teaches inulin and starch as obvious natural polymer equivalents. It would be obvious to one of ordinary skill in the art to modify Leo with teachings of Guttag and Tomka in order to provide a toy/chewable article because it is easily broken down by natural decay bacteria.

10. With regard to claim 13, Leo discloses a chew toy for animals in the shape of a dog bone (abstract).

11. With regard to claim 14, Leo discloses a chew toy for animals comprising a starch material and a biodegradable thermoplastic polymer. The thermoplastic blend is obtained by processing starch and thermoplastic polymer in the presence of water or plasticizer (col 1 lines 33-37). However, Leo failed to disclose Inulin. Guttag teaches biodegradable plastic articles such as toys (col 3 lines 40-44) comprising a synthetic plastic polymer, a natural polymer and a polymer-attacking agent. The natural polymers are found in nature and are easily broken down by natural decay bacteria. It includes but is not limited to particles of starch, inulin, cellulose and wood (col 2 lines 31-34). This suggests that starch and inulin are obvious equivalents as natural polymers and one of ordinary skill in the art would be able to utilize inulin instead of starch in forming a toy/chewable article because it is easily broken down by natural decay bacteria.

Conclusion

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Prior art discloses applicable subject matter.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Adepeju Pearse whose telephone number is 571-272-8560. The examiner can normally be reached on Monday through Friday, 8.00am - 4.30pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Milton Cano can be reached on 571-272-1398. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



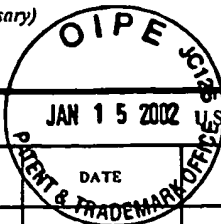
Peju Pearse



MILTON J. CANO
SUPERVISORY PATENT EXAMINER
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INFORMATION DISCLOSURE CITATION

(Use several sheets if necessary)



Docket Number (Optional)

C1392 5669

Application Number

09/936,534

Applicant(s)

Catia BASTIOLI, et al.

Filing Date

September 14, 2001

Group Art Unit

To be Assigned

U.S. PATENT DOCUMENTS							
EXAMINER INITIAL	REF	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

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TC 1700

FOREIGN PATENT DOCUMENTS

	REF	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	Translation	
							YES	NO
AP		WO 99/30691	6/1999	WIPO				✓

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

AP	Jongboom, R.O.J., et al., "Inulin as a Thermoplastic Matrix Material for Encapsulation", Proceedings Book of the 26th International Symposium on Controlled Release of Bioactive Materials, June 1999 (1999-06) pp. 263-264, XP000913601.

EXAMINER /Adepeju Pearse/ (05/02/2006)	DATE CONSIDERED
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EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP Section 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Notice of References Cited

Application/Control No.

09/936,534

Applicant(s)/Patent Under

Reexamination

BASTIOLI ET AL.

Examiner

Adepeju Pearse

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Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-6,313,203	11-2001	Van Haveren et al.	524/58
*	B	US-5,346,929	09-1994	Guttag, Alvin	523/124
*	C	US-6,054,166	04-2000	Dupart, Pierre	426/549
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N	WO 98/52578	11-1998	Europe	Van Loo et al	
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/715	A1	(11) International Publication Number: WO 98/52578 (43) International Publication Date: 26 November 1998 (26.11.98)
(21) International Application Number: PCT/EP98/02864 (22) International Filing Date: 14 May 1998 (14.05.98) (30) Priority Data: 97870069.8 20 May 1997 (20.05.97) EP (34) Countries for which the regional or international application was filed: BE et al. (71) Applicant (for all designated States except US): TIENSE SUIKERRAFFINADERIJ N.V. [BE/BE]; Tervurenlaan 182, B-1150 Brussel (BE). (72) Inventors; and (75) Inventors/Applicants (for US only): VAN LOO, Jan [BE/BE]; Lepelstraat 3, B-3000 Leuven (BE). FRIPPIAT, Anne [BE/BE]; Abelooslaan 14, B-1933 Sterrebeek (BE). (74) Agent: HERMANS, Johnny; Tiense Suikerraffinaderij N.V., Aandorenstraat 1, B-3300 Tienen (BE).		(81) Designated States: AU, CA, CN, ID, JP, KR, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: FRUCTAN CONTAINING COMPOSITION FOR THE PREVENTION AND TREATMENT OF COLON CANCER (57) Abstract The use is provided of a fructan with an average degree of polymerisation of at least 15 for the manufacture of a composition for the prevention and/or treatment of colon cancer in non-bovine mammals, particularly in human beings. Also provided is a method of prevention and treatment of colon cancer in a non-bovine mammal, particularly in a human being, comprising administering to said mammal a composition comprising an effective dose of a fructan with an average degree of polymerisation of at least 15. The said composition can be a medicament as well as a functional food. In a preferred embodiment the fructan is inulin, more preferably inulin with an average degree of polymerisation of at least 20.		

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FRUCTAN CONTAINING COMPOSITION FOR THE PREVENTION AND TREATMENT OF COLON CANCER

5

Field of the invention.

The present invention relates to the use of certain fructans, preferably certain inulins, for the manufacture of a composition for the prevention and/or treatment of colon cancer in non-bovine mammals.

10

The present invention also relates to the use of compositions comprising certain fructans, preferably certain inulins, for the prevention and/or treatment of colon cancer in non-bovine mammals, and to a method of prevention and/or treatment of colon cancer in non-bovine mammals.

15

Background of the invention.

Cancer in mammals is a disease which is already known from Ancient Times. Nowadays cancer, particularly lung, breast and colon cancer, has become one of the major causes of death of non-bovine mammals, in particular of humans, in the industrialised world.

20

The cancer disease is known to proceed in several steps, including genesis of cells of modified genome and functionality resulting in the formation of malignant cells; uncontrolled local proliferation of the malignant cells and invasion of adjacent normal body structures; and metastasis. During metastasis malignant cells are spread in a body cavity and/or throughout the body via the blood stream and/or the lymph, with invasion of various normal body structures. The invasion of the normal body structures results in their malfunctioning and/or destruction, eventually leading to the death of the affected mammal.

25

Various factors which can provoke carcinogenesis and cancer have already been identified, including certain viral infections, exposure to ionising radiation, exposure to certain mineral fibres, exposure to chemical mutagens, and improper diet.

30

As a result thereof various preventive measures have been introduced which have shown to be successful in preventing or reducing the occurrence of certain cancers.

35

Furthermore, various surgical and chemotherapeutical methods have been developed for the treatment of cancer. According to the type of cancer, the stage of the disease and the particulars of the affected mammal, these methods have been shown effective to a more or lesser degree.

5 Many reliable animal models for the study of the genesis and evolution of various cancers are available at present, enabling the evaluation of the preventive and curative properties of miscellaneous chemicals and dietary products.

10 Epidemiological studies in combination with studies on animal models have lead to the identification of dietary fibres as an important factor in the prevention and inhibition of certain cancers in mammals.

Dietary fibres are commonly defined as components of plant cells which are resistant to hydrolysis by the alimentary enzymes of man. Dietary fibres comprise cellulose, hemicellulose, polysaccharides, pectin, gums, waxes and lignin. According to this definition, fructans, which are soluble and edible polysaccharides, are dietary fibres. Fructans are composed of chains of carbohydrates which consist mostly of fructose units and in which fructosyl-fructose linkages constitute the majority of the linkages. Fructans commonly occur as polydisperse carbohydrates. They occur in plants, but they also can originate from bacterial activity and they can be synthesised enzymatically as well. All these fructans present typical dietary fibre properties; they are embraced by the present invention and are referred to herein as fructan(s).

25 Fructans are well known compounds including levan and inulin carbohydrates. Levans are D-fructans generally consisting of chains of fructose units which are essentially connected to each other by $\beta(2-6)$ linkages. Inulins are also D-fructans generally consisting of chains of fructose units but which are essentially connected to each other by $\beta(2-1)$ linkages. Most of the inulin chains terminate in one glucose unit.

30 Levans may occur as linear chain carbohydrates but they are mostly composed of branched fructose chains, whereas inulins are generally composed of linear chain carbohydrates but they may also occur as chains of fructose units which are branched to a larger or lesser extent. Levans and inulins which are suitable according to the present invention include linear and branched chain carbohydrates, as well as mixtures of said linear and branched chain carbohydrates.

35

Inulins occur in many plants and crops and can occur at concentrations of about 10 to 20 % on fresh weight in chicory, dahlia tubers and Jerusalem artichoke. They can be isolated from these plants, purified, and optionally refined to remove impurities and undesired fractions of carbohydrates, at industrial scale, according to well known techniques.

Inulins can be represented by the general formulae GF_n and F_m wherein G represents a glucose unit, F represents a fructose unit, n represents the number of fructose units linked to the terminal glucose unit, and m represents the number of fructose units linked to each other in the carbohydrate chain.

The number of saccharide units (fructose and glucose units) in one fructan molecule, i.e. the values $n+1$ and m in the above formulae, are commonly referred to as the degree of polymerisation and represented as (DP). Often the parameter average degree of polymerisation (\overline{DP}) is used too, which is the value corresponding to the total number of saccharide units divided by the total number of saccharide molecules present in a given (poly)saccharide composition.

Inulin from plant origin is a polydisperse composition of fructose chains with a degree of polymerisation (DP) ranging from 2 to about 100, whereas inulin from bacterial origin usually has a higher degree of polymerisation.

Fructans, including inulins of general formulae GF_n and F_m , with a lower degree of polymerisation, usually defined as a $(DP) < 10$, are commonly named oligofructoses and are referred to herein accordingly.

Inulin is commercially available. For example, inulin from chicory is available as RAFTILINE® from ORAFTI, (Tienen, Belgium), in various grades. Typical RAFTILINE® grades are, for example, ST, ST-Gel and GR (which have an average degree of polymerisation (\overline{DP}) of 10 and contain in total about 8 % by weight glucose, fructose and sucrose), LS (which has also an average degree of polymerisation of 10 but which contains in total less than 1 % by weight glucose, fructose and sucrose), and HP (high performance inulin) and HP-Gel (which have an average degree of polymerisation of ≥ 23 , commonly about 25, and are essentially free of glucose, fructose and sucrose).

Oligofructoses are usually obtained by partial, acidic or enzymatic hydrolysis of inulins and can also be obtained by enzymatic synthesis from sucrose, according to techniques which are well-known in the art.

Oligofructoses are commercially available. Several grades of oligofructose are, for example, available from ORAFTI, (Tienen, Belgium), as RAFTILOSE®, e.g. RAFTILOSE® P95 which contains about 95 % by weight oligofructoses with a degree of polymerisation ranging from 2 to 7 and about 5 % by weight in total of glucose, fructose and sucrose.

State of the art.

Dietary fibres, in particular fructans, are known to have effects on various physiological functions and mechanisms in mammals.

In non-bovine mammals, these fibres are almost not metabolised in the mouth, the stomach and the small intestine, and they thus almost quantitatively enter the large intestine where they are completely fermented by the colonic microflora. This phenomenon results in various beneficial health effects in non-bovine mammals such as, for example, a reduction of the intestinal transit time, a decrease of the intestinal pH, a bifidus stimulating activity in the colon, an increase of the stool weight (bulking) and stool frequency.

Fructans, particularly inulin, are also known to have a beneficial effect on lipid metabolism, including a lowering effect on blood cholesterol and on serum triglycerides, and an increasing effect on the HDL/LDL ratio.

P.D. Cooper et al., *Molecul. Immunol.*, **23** (8), 895, (1986), describe the activation of the alternative pathway of complement by gamma-inulin (a specific polymorphic form of dahlia inulin), and it is known that an activator of the alternative pathway of complement can have a potential non-specific anti-tumour effect.

Furthermore, fructans, particularly inulin, are described to have potential in the prevention and inhibition of cancer.

P.D. Cooper et al., (*Molecul. Immunol.*, **23** (8), 903, (1986) have demonstrated that intraperitoneally injected gamma-inulin can prolong the survival of melanoma bearing mice.

It has also been disclosed that cultures of bifidobacteria inhibit 2-amino-3-methyl-imidazol[4,5-f]quinoline induced colon, liver, and mammary carcinogenesis (B.S. Reddy et al., *Cancer Res.*, **53**, 3914-3918, (1993) and azoxymethane-induced colon carcinogenesis (N. Kulkarni et al., *Proc. Soc. Exptl. Biol. Med.*, **207**, 278-283, (1994) in rats.

European patent application EP 0 692 252 A1 discloses the suppressing effect of the oligofructose RAFTILOSE® P95 (ex ORAFTI,

Belgium; consisting of 95 % of oligofructose chains with a degree of polymerisation (DP) between 2 and 7) and of the inulins RAFTILINE® ST, GR and LS, (defined hereinbefore and having an average degree of polymerisation of about 10) on breast carcinogenesis induced by injection of N-methylnitrosourea (MNU) in rats as well as on the growth of the transplantable TLT tumour (Taper Liver Tumour) in mice. The investigated oligofructose and inulins showed to have about equal carcinogenesis protective and cancer inhibiting effects.

Furthermore, the relation between the intake of dietary fibres and the reduction of the risk of colon cancer has been disclosed in several publications, e.g. J. Potter et al., Principles of Chemoprevention, IARC Scientific Publication N° 139, 61-90, (1996); G.R. Howe et al., J. Natl. Cancer Inst., 84, 1887-1896, (1992); and B.S. Reddy et al., Gastroenterol., 102, 1475-1482, (1992).

However, in spite of the enormous efforts already made in the fight against cancer diseases, and colon cancer in particular, the prevention and successful inhibition and curing of colon cancer is not always possible yet. Therefore, Medicine is still looking for improving the prevention, inhibition and curing of colon cancer. For various reasons such as the patient's comfort, chemotherapeutical methods are most preferred. Accordingly, there is a continuously ongoing search for improved and/or alternative compositions and therapeutical methods presenting a beneficial effect with respect to the inhibition and/or treatment of colon cancer, and /or presenting less undesirable side effects compared to known compositions and therapeutical methods.

Description of the invention.

The applicant is providing by the present invention a solution to one or more of the above mentioned problems, which even may present additional advantages.

By the term colon cancer is meant herein the colon cancer disease in any of its steps, including colon carcinogenesis, the formation of malignant cells in the colon, proliferation of said malignant cells and formation of tumours in the colon and /or invasion of normal colon structures by said malignant cells.

The invention is based on the findings made by the inventors during extensive studies that fructans with a higher degree of

polymerisation, in particular fructans having an average degree of polymerisation of 15 or higher, present improved preventive and inhibiting properties against colon cancer in non-bovine mammals compared to fructans with a lower degree of polymerisation.

5 In view of the prior art, it could be expected that fructans with a higher degree of polymerisation, could, as do certain fructans with a lower degree of polymerisation, have preventive and/or inhibitive properties against colon cancer. However, the surprising findings of the inventors that
10 fructans, in particular inulins, with a higher average degree of polymerisation, present significantly enhanced preventive and inhibiting properties against colon cancer in non-bovine mammals, compared to fructans with a lower average degree of polymerisation, could not be expected at all having regard to the state of the art.

Accordingly, in one aspect, the present invention relates to the use
15 of a fructan with an average degree of polymerisation of at least 15 for the manufacture of a composition for the prevention and/or treatment of colon cancer in non-bovine mammals, particularly in human beings.

In another aspect, the invention relates to the use of a composition comprising a fructan with an average degree of polymerisation of at least 15,
20 for the prevention and/or treatment of colon cancer in non-bovine mammals, particularly human beings.

In a further aspect, the invention relates to a method for the prevention and/or treatment of colon cancer in non-bovine mammals, particularly human beings, by administering to said mammal susceptible of
25 colon cancer, in need of such prevention or treatment, a composition comprising an effective dose of a fructan with an average degree of polymerisation of at least 15.

In one preferred embodiment, the fructan is levan, preferably with an average degree of polymerisation of at least 20, more preferably ranging
30 from 20 to 50.

In another preferred embodiment, the fructan is inulin, preferably with an average degree of polymerisation of at least 20, even more preferably ranging from 20 to 70. In a further preferred embodiment, the inulin has an average degree of polymerisation ranging from 20 to 40. A typically
35 preferred inulin has an average degree of polymerisation about 25.

Inulin essentially consisting of linear polysaccharide chains or inulin containing up to about 2 % by weight branched polysaccharide chains,

are suitable according to the invention, but inulin containing a higher percentage of branched chains and even inulin essentially consisting of branched polysaccharide chains, and even mixtures of said linear and branched inulins, are suitable as well according to the invention. Typical
5 inulins suitable according to the present invention are chicory inulins, for example RAFTILINE® HP and RAFTILINE® HP-Gel (both high performance inulins [in short HP inulin] ex ORAFTI, Belgium), with an average degree of polymerisation of about 25.

By the term composition according to the present invention is
10 meant herein a medicament, (i.e. a composition which has a prophylactic and/or a curative effect on a mammal to which it has been administered), as well as a functional food, (i.e. a food product for human beings or for a non-human mammal, containing an additional functional ingredient, and which
15 apart from its nutritional properties, additionally provides to that being one or more beneficial physiological effects). In the functional food compositions according to the present invention, said additional functional ingredient is meant to be a fructan, including levans and inulins, as defined herein before. Typical beneficial physiological effects are, for example, beneficial effects on
20 the digestive tract, effects on lipid metabolism and preventive effects against cancer, in particular colon cancer.

When, in accordance with the present invention, the composition is a medicament, it can consist of the defined fructan or it can comprise said fructan in combination with any pharmaceutically acceptable carrier, and optionally also in combination with one or more physiologically active
25 compounds, drugs or prodrugs. Said medicament can have any form known in the art, and can be administered according to known methods. Preferably, the medicament is in the form of a powder, a tablet, a soft gel capsule, a syrup, a solution or a suspension, and is administered orally. However, when present in an appropriate galenic form, the composition can also be
30 administered parenterally, via tube feeding or rectally.

When the composition according to the present invention is a functional food, it is orally administered and it can be present in any known food form, such as, for example, a table spread, a dairy product such as e.g. a milk, a dairy dessert, a yoghurt, or a cheese, an alcoholic or non-alcoholic
35 drink, a bakery product, a chocolate, an ice cream, a meat product, a fruit preparation, a confectionery product, a cereal product, a sauce, a soup, a snack, a dry mix, a meal replacer, a pet food, and the like.

The daily dosis effective in providing prevention against colon cancer preferably ranges, depending from the mammal species and the fructan species, from 0.01 to 2 g/kg body weight, more preferably from 0.05 to 0.5 g/kg body weight.

5 The daily dosis effective in providing an inhibitive and/or curing effect on colon cancer preferably ranges, depending from the mammal species, the fructan species and the stage of development of the colon cancer, from 0.2 to 3 g/kg body weight, more preferably from 0.5 to 1.5 g/kg body weight.

10 In the method of prevention and/or treatment, including inhibition and/or curing, of colon cancer in non-bovine mammals, preferably human beings, the daily dose of the composition according to the present invention described hereinbefore, can be administered to a said mammal susceptible of colon cancer and in need for such treatment, according to
15 known methods in one or more unit doses during a shorter or longer period of time, in function of strength of the effect provided by the composition. When the composition is a functional food and a preventive effect is aimed at, the functional food is advantageously administered in one or more forms over a longer period of time, most preferably during the whole lifetime of the
20 mammal.

 Besides the improved physiological, prophylactic and/or therapeutical effects of the fructans with a higher degree of polymerisation compared to fructans with a lower degree of polymerisation, the compositions and method of treatment according to the present invention
25 present significantly additional advantages. The compositions, for example, are easy to take in or to administer, and the method of treatment is easy to apply, without significant discomfort for the concerned mammal. Furthermore, the presence of fructan chains with a higher degree of polymerisation reduces certain discomforts often encountered with the
30 intake of non-digestible carbohydrates such as e.g. soft stools, diarrhea, flatulence, bloating and intestinal cramps.

 A further considerable advantage presented by the fructans, in particular the preferred chicory inulin, relating to the present invention, is that they are naturally occurring, biodegradable products which are deprived of toxic
35 effects and that they can be taken in and administered to newborn as well as adult, including pregnant, and aged mammals. Compared to many known chemo-therapeutical compositions, the intake of, administration of, and the

treatment with a composition comprising the above defined fructans according to the present invention, is usually very well supported by the mammal and does not provoke significant undesirable side effects or a significant discomfort, if any at all, to the mammal. Furthermore, the fructans suitable according to the present invention are largely commercially available at acceptable cost.

Experimental part.

In support of the present invention, the following illustrative experimental data are given regarding a study made to determine the effect of oligofructose and HP inulin on carcinogen-induced colonic aberrant crypt foci (ACF) formation in rat.

Aberrant crypt foci (ACF), which are recognized as early preneoplastic lesions in the colon, have consistently been observed in experimentally induced colon carcinogenesis in laboratory animals (McLellan, E.A. et al., *Cancer Res.*, 51, 5270-5274, (1991) and Wargovich, M.H., et al., *Cancer Epidemiol Biomarkers & Prev.*, 5, 355-360, (1996)).

Pretlow, T.P., et al., *J. Cell. Biochem.*, 16G (Suppl.), 55-62, (1992), have also shown that these lesions are present in the colonic mucosa of patients with colon cancer and have suggested that aberrant crypts are putative precursor lesions from which adenomas and carcinomas may develop in the colon. ACF express mutations in the *apc* gene and *ras* oncogene that appear to be biomarkers of colon cancer development (Vivona, A.A., et al., *Carcinogenesis* (Lond.) 14, 1777-1781, (1993)).

There is some evidence that several inhibitors of ACF formation reduce the incidence of colon tumors in laboratory animals (Wargovich, M.H., et al., *Cancer Epidemiol Biomarkers & Prev.*, 5, 355-360, (1996)), suggesting that ACF induction can be used to evaluate novel agents for their potential chemopreventive properties against colon cancer.

MATERIALS AND METHODS

Animals, diets, carcinogen, and chemopreventive agents.

5 Azoxymethane (AOM) was obtained from Ash Stevens (Detroit, MI, USA). RAFTILOSE® P95 and RAFTILINE® HP which contained on dry matter mainly oligofructose (95%) and inulin (99.5%), respectively, were obtained from ORAFIT (Tienen, Belgium). RAFTILOSE® which was produced by partial enzymatic hydrolysis of chicory inulin is a polydisperse β [2-1] fructan with a (DP) ranging between 2 and 7 and a (\overline{DP}) of 4.5.
10 RAFTILINE® HP (i.e. high performance inulin and abbreviated herein to HP inulin) is chicory inulin of which the lower (DP) fraction has been removed. Its (DP) ranges between 10 and 60 and it has a (\overline{DP}) of 25. This choice of test substrates thus allows to observe effects of the degree of polymerisation.

Weanling male F344 rats were obtained from Charles River Breeding Laboratories (Kingston, NY, USA). All ingredients of the AIN-76A semipurified diet were obtained from Dyets Inc., (Bethlehem, PA, USA) and were stored at 4°C until the experimental diets were prepared. The percentage composition of semipurified diet is as follows : casein, 20; D,L-methionine, 0.3; corn starch, 52; dextrose, 13; corn oil, 5; alphacel, 5; mineral
20 mix (AIN-76A), 3.5; vitamin mix (AIN-76A), 1; and choline bitartrate, 0.2 (Reddy B.S., et al., *Cancer Res.*, 48, 6642-6647, (1988). The rats were held in quarantine for 1 week and had access to modified AIN-76A semipurified control diet. They were randomly distributed by weight into various dietary groups and were transferred to an animal holding room where they were housed in plastic cages, three rats/cage, under controlled conditions of a 12 h
25 light/ 12 h dark cycle, 50% relative humidity, and 21°C room temperature. RAFTILOSE® and RAFTILINE® were added to the control diet at 10% level at the expense of starch.

Experimental procedure. Beginning at 5 weeks of age, groups of
30 animals were fed the control or experimental diets. All animals except the vehicle-treated rats received AOM s.c. once weekly at 7 and 8 weeks of age at a dose rate of 15 mg/kg body weight/week. Animals intended for vehicle treatment were given an equal volume of normal saline. The rats were continued on control or experimental diets until the termination of the study,
35 when they were 16 weeks of age. All animals were sacrificed by CO₂ euthanasia. The colons were removed, flushed with Krebs-Ringer solution, opened from cecum to anus, and fixed flat between two pieces of filter paper

in 10% buffered formalin. After a minimum of 24 h in buffered formalin, the colons were cut into 2-cm segments, placed in a Petri dish containing 0.2% methylene blue in Krebs-Ringer solution and kept for 5-10 min. They were then placed, mucosal side up, on a microscope slide and observed through a light microscope. ACF were recorded according to standard procedures (McLellan E.A., et al., *Cancer Res.*, 51, 5270-5274, (1991).

Aberrant crypts were distinguished from the surrounding normal crypts by their increased size, significantly increased distance from lamina to basal surface of cells, and the easily discernible pericryptal zone. Crypt multiplicity was determined as the number of crypts in each focus and categorised as those containing up to three, or four or more aberrant crypts/focus. All colons were scored by one observer without knowing the identity of agents under study; scores were checked at random by a second observer.

Statistical Analysis. All results were expressed as the means \pm SD and were analysed by one-tailed Student's *t*-test. Differences were considered statistically significant at $p < 0.05$.

RESULTS

General Observations. The body weights of AOM-and vehicle-treated animals fed the control and experimental diets containing 10% inulin or oligofructose were comparable throughout the study (Table 1, hereafter). There were no signs of any adverse effects in liver, kidney, stomach, intestine or lungs of animals fed inulin or oligofructose.

Aberrant Crypt Foci. Table 2 hereafter summarises the AOM-induced ACF in the colon of rats fed the control and experimental diets. The animals administered saline (vehicle) and fed the control and experimental diets containing inulin or oligofructose showed no evidence of ACF formation in the colon (data not shown). In the animals fed the control diet, AOM treatment induced on the average about 120 ACF/colon. ACF were predominantly observed in the distal colons. Efficacy end points used in this study were inhibition of the total number of ACF/colon as well as the reduction of the number of multicrypt clusters (2 or more) of aberrant crypts/focus. Administration of oligofructose or HP inulin in the diet significantly suppressed the total number of ACF/colon as compared to the control diet; the degree of inhibition was significantly more pronounced in the animals fed HP inulin ($p < 0.006$) than in those fed oligofructose ($p < 0.02$).

Crypt multiplicity in terms of 2 or 3 aberrant crypts/focus was also significantly inhibited in animals fed HP inulin ($p < 0.02 - 0.0001$) or oligofructose ($p < 0.04 - 0.01$).

5 Because multiplicity of aberrant crypts has been a probable predictor of colon tumor outcome (Pretlow, T.P., et al., *Carcinogenesis* (Lond.), 13. 1509-1512, (1992)), the present study used this criterion to evaluate oligofructose and HP inulin for their potential inhibitory properties.

10 The results of the present study indicate that orally taken oligofructose and HP inulin inhibits AOM-induced colonic ACF formation in rats supporting the potential colon tumor inhibitory properties of chicory fructans. The experimental results clearly demonstrate that the preventive and ACF inhibitory properties provided by a fructan (*in casu* HP inulin) with a higher average degree of polymerisation, are considerably enhanced compared to a
15 fructan (oligofructose) with a lower average degree of polymerisation.

Table 1. Body weights of animals fed the control diet and experimental diets containing oligofructose and HP inulin.

Experimental groups	Body weights (grams) on control and experimental diets at week			
	0	3	6	10
<u>AOM-treated</u>				
1. Control diet	119 ± 5.9 ^a	173 ± 9.1	257 ± 11	320 ± 14
2. Oligofructose, 10%	119 ± 6.6	167 ± 9.8	258 ± 15	327 ± 16
3. HP Inulin, 10%	120 ± 7.1	73 ± 7.8	259 ± 12	328 ± 15
<u>Saline-treated</u>				
4. Control diet	117 ± 8.5	179 ± 9.7	256 ± 9.8	329 ± 12
5. Oligofructose, 10%	120 ± 5.9	175 ± 7.3	264 ± 9.3	338 ± 12
6. HP Inulin, 10%	119 ± 5.7	171 ± 6.0	256 ± 8.1	329 ± 13

^a Mean ± SD

Table 2. Effect of dietary oligofructose and HP inulin on colonic ACF formation in male F344 rats.

Experimental groups	Total ACF/colon	Foci containing number of aberrant crypts			
		1 crypt/focus	2 crypts/focus	3 crypts/focus	4 or more crypts/focus
Control diet	120 ± 28	19.5 ± 7.3	43.7 ± 7.8	28.2 ± 7.5	28.3 ± 8.2
Oligofructose, 10%	92 ± 28 ^b (p<0.024)	15.4 ± 7.5	31.2 ± 13 ^b (p<0.01)	21.3 ± 7.8 ^b (p<0.04)	23.9 ± 8.2
HP Inulin, 10%	78 ± 37 ^b (p<0.006)	15.7 ± 8.2	24 ± 12 ^b (p<0.0001)	16.6 ± 7.2 ^b (p<0.02)	21.8 ± 14.2

^a Mean ± SD^b Significantly different from the control diet. The level of significance is shown in parenthesis.

CLAIMS

- 5 1. Use of a fructan with an average degree of polymerisation of at least 15 for the manufacture of a composition for the prevention and/or treatment of colon cancer in non-bovine mammals.
2. Use according to claim 1 wherein the mammal is selected from the group consisting of a human being, a dog and a cat.
- 10 3. Use according to any of claims 1 or 2 wherein the fructan is a levan.
4. Use according to claim 3 wherein the levan has an average degree of polymerisation of at least 20.
5. Use according to any of claims 1 or 2 wherein the fructan is an inulin.
- 15 6. Use according to claim 5 wherein the inulin has an average degree of polymerisation of at least 20.
7. Use according to claim 6 wherein the inulin is chicory inulin with an average degree of polymerisation of about 25 and which is essentially free of glucose, fructose and sucrose.
- 20 8. Use according to any of claims 1 to 7 wherein the composition is a medicament.
9. Use according to claim 8 wherein the medicament comprises said fructan in combination with a pharmaceutically acceptable carrier and optionally with a physiologically active compound, a drug or a pro drug.
- 25 10. Use according to any of claims 1 to 7 wherein the composition is a functional food.
11. Use of a composition as defined in any of claims 1 to 10 for the prevention and/or treatment of colon cancer in a non-bovine mammal.
- 30 12. Method of prevention of colon cancer in a non-bovine mammal comprising administering to said mammal susceptible of colon cancer in need of such treatment, a composition comprising an effective dose of a fructan with an average degree of polymerisation of at least 15.
13. Method according to claim 12 wherein the daily dose of fructan administered in one or more unit doses, ranges from 0.01 to 2 g/kg body weight.
- 35 14. Method of treatment of colon cancer in a non-bovine mammal comprising administering to said mammal in need of such treatment, a

composition comprising an effective dose of a fructan with an average degree of polymerisation of at least 15.

5 15. Method according to claim 14 wherein the daily dose of fructan administered in one or more unit doses, ranges from 0.2 to 3 g/kg body weight.

16. Method according to any of claims 12, 13, 14 or 15 wherein the mammal is selected from the group consisting of a human being, a dog and a cat.

10 17. Method according to claim 16, wherein the fructan is a levan.

18. Method according to claim 16 wherein the fructan is an inulin.

19. Method according to claim 18 wherein the inulin has an average degree of polymerisation of at least 20.

15 20. Method according to claim 19 wherein the inulin is chicory inulin with an average degree of polymerisation of about 25 and which is essentially free of glucose, fructose and sucrose.

21. Method according to any of claims 12 to 20 wherein the composition is a functional food.

20 22. Method according to any of claims 12 to 20 wherein the composition is a medicament.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/02864

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/715

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HAMBLY ET AL.: "Effects of high and low risk diets on biomarkers of colon cancer in human-flora-associated (HFA) rats" ANTICANCER RESEARCH, vol. 15, no. 5a, 1995, pages 1656-1657, XP002046243 see abstract no 83	1-22
Y	EP 0 692 252 A (RAFFINERIE TIRLEMONTTOISE SA) 17 January 1996 cited in the application see in particular claims 1-12, examples 3,4,7	1-22



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/02864

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN vol. 014, no. 439 (C-0761), 19 September 1990 & JP 02 172921 A (NITTO DENKO CORP), 4 July 1990, see abstract	1-22
A	PATENT ABSTRACTS OF JAPAN vol. 009, no. 228 (C-303), 13 September 1985 & JP 60 089427 A (DAINIPPON SEIYAKU KK), 20 May 1985, see abstract	1-22
A	PATENT ABSTRACTS OF JAPAN vol. 012, no. 333 (C-526), 8 September 1988 & JP 63 093729 A (SEKISUI CHEM CO LTD), 25 April 1988, see abstract	
A	GIBSON ET AL.: "Selective stimulation of bifidobacteria in the human colon by oligofructose and inulin" GASTROENTEROLOGY, vol. 108, no. 4, 1995, pages 975-82, XP002046244 see the abstract, and penultimate paragraph at page 981	1-22
P,X	REDDY ET AL.: "Effect of dietary oligofructose and inulin on colonic preneoplastic aberrant crypt foci inhibition" CARCINOGENESIS, vol. 18, no. 7, July 1997, pages 1371-1374, XP002046245 see the whole document	1-22
P,X	ROWLAND ET AL.: "Effect of Bifidobacterium longum and inulin on gut bacterial metabolism and carcinogen-induced aberrant crypt foci in rats" CARCINOGENESIS, vol. 19, no. 2, February 1998, pages 281-285, XP002076980 *see in particular the abstract*	1-22

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/02864

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0692252 A	17-01-1996	US 5721345 A	24-02-1998

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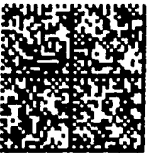
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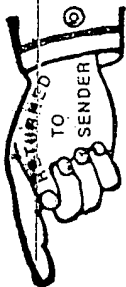
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